Review

Risk of Non-Hodgkin's Lymphoma and Family History of Lymphatic, Hematologic, and Other Cancers

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Abstract

Background: An elevated risk of developing non-Hodgkin's lymphoma (NHL) has been associated with a family history of NHL and several other malignancies, but the magnitude of risks and mechanisms are uncertain. Methods: We used self-reported family history data from a recent multicenter U.S.-based case-control studies of NHL to evaluate familial aggregation of NHL with various hematolymphoproliferative and other cancers. Estimates of familial aggregation were obtained as hazard ratios (HR) that compare incidence of different cancers in first-degree relatives of NHL cases with that in the first-degree relatives of NHL controls. Limitations of the study included low participation rates (76% for cases and 52% for controls) and potential differential accuracy of recall. Results: Risk of NHL was elevated in relatives of NHL cases [HR, 2.9; 95% confidence interval (95% CI), 0.95–8.53]; the aggregation seems to be stronger for siblings (HR, 7.6; 95% CI, 0.98–58.8) and for male relatives (HR, 6.2; 95% CI, 0.77–50.0). Risk of Hodgkin's lymphoma seems to be also elevated among relatives of early-onset (<50 years) NHL cases (HR, 3.2; 95% CI, 0.88–11.6). Evaluation of family history of other cancers provided modest evidence for an increased risk of melanoma of the skin (HR, 2.9; 95% CI, 1.08–7.75), pancreatic cancer (HR, 2.1; 95% CI, 0.96–4.43), stomach cancer (HR, 1.8; 95% CI, 0.91–3.63), and prostate cancer (HR, 1.3; 95% CI, 0.87–1.99). Conclusions: These results are consistent with previous findings of familial aggregation of NHL, Hodgkin's lymphoma, and a few other cancers. The pattern of male-specific and sibling-specific familial aggregation of NHL we observed, if confirmed, may shed new light on the possible mechanisms that underlie familial aggregation of the disease. (Cancer Epidemiol Biomarkers Prev 2004;13(9):1415–21)

Introduction

Over the last several decades in the United States, the annual age-adjusted incidence rate (per 100,000 person years) of non-Hodgkin's lymphoma (NHL) has increased >75% from 11.1 in 1975 to 19.8 in 1995 (1). Since 1995, the incidence has remained relatively steady. Although the exact cause of this increase has not been determined, some evidence has accumulated to suggest that most of this increase is real rather than a simple artifact of diagnosis or classification (2).

Against this backdrop of changing incidence patterns, relatively little is known regarding the etiology of NHL. Several viruses are involved in the etiology of specific rare subtypes of NHL, such as human T-cell lymphotrophic virus I and adult T-cell leukemia/lymphoma (3, 4). Immune dysfunction/suppression substantially increases the subsequent risk of NHL (5). In addition, people with a history of malignant disease seem to be at increased risk of NHL (6-8). However, these known risk factors account for only a small proportion of the total NHL cases that occur annually in the United States.

There is mounting evidence that a family history of hematolymphoproliferative cancers is associated with an increased risk of NHL (9-15). Other studies, designed primarily to evaluate other risk factors, have suggested that a family history of lymphatic or hematologic cancer modifies the effects of alcohol (9), vitamin C and carotene (16), pesticides (17), and homosexual behavior and heroin use (18) on the subsequent development of NHL. These findings underline the importance of furthering our understanding of the exact role that family history of cancer plays in the development of NHL.

This article reports on a population-based case-control study of NHL conducted within the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Our primary goal was to measure the extent and heterogeneity of familial aggregation of NHL. We

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also estimated the co-occurrence of NHL with other hematolymphoproliferative cancers within families and explored the possible familial aggregation with solid tumors.

Methods

The study population comprised four areas of the United States served by National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results registries: the Detroit metropolitan area (Macomb, Oakland, and Wayne Counties), 13 contiguous counties in northwestern Washington State, the state of Iowa, and Los Angeles County (1). Each of the four Surveillance, Epidemiology, and End Results registries identified all residents ages 20 to 74 years who had a first primary diagnosis of NHL. All cases were histologically confirmed and were coded at each registry according to the *International Classification of Diseases for Oncology, Second Edition*. Based on these codes, four NHL subtypes were defined (diffuse, follicular, T cell, and all other) without further central review. HIV-infected cases were excluded from study.

Eligible cases were residents newly diagnosed during the period from July 1, 1998 to June 30, 2000 who were alive and competent to participate. In Iowa and Seattle, all consecutive cases were chosen. In Los Angeles and Detroit, all African American cases and a random sample of White cases were eligible for study, allowing for oversampling of African American cases than would arise in a simple series. Cases were identified through rapid reporting mechanism at each registry. Study staff sent a letter to the patient's attending physician explaining the study and the eligibility criteria. In some instances, the physician requested that the patient not be contacted (physician refusal).

Population controls were selected from area residents ages 20 to 74 years with no previous diagnosis of NHL or HIV infection. To select controls under age 65 years, we used one-step list-assisted random digit dialing (19). Accounting for nonworking numbers, we calculated that 78.5% of the telephone numbers belonging to residences yielded a roster of individuals in the household. From these households, we selected potential controls at random, stratified on geographic area, age, and race. Controls ages 65 to 74 years were identified from Medicare eligibility files.

Data collection included multiple components. Before the home visit, subjects were mailed a form for recording their residences and jobs year by year and one of two self-administered questionnaires. All African American subjects and half of other subjects were sent a detailed family and medical questionnaire, the basis of the present analysis, whereas the others were sent a dietary questionnaire. During the home visit, the interviewer collected carpet dust, a blood or saliva sample, and (from a few subjects in Iowa on private wells) drinking water samples and administered one of two versions of a computer-assisted personal interview, corresponding to the two forms of the self-administered questionnaire. Subjects who had received the detailed self-administered family history questionnaire were queried on personal medical history and illicit drug use. Subjects who had received the dietary questionnaire were queried on an abbreviated medical and family history, sunlight exposures, cell phone use, allergies, and hobbies. All respondents were asked a core set of questions: demographic characteristics, hair coloring, occupational history, and a detailed history of residences occupied since 1970. Subjects were given a cash token of appreciation for their participation (varying from 5 to 50 dollars depending on location). Pathology specimens were sought for all cases.

Written informed consent was obtained during the home visit. Participants were asked if they wished to participate in each study component; separately, that is, for interview, blood sample, buccal sample, dust sample, and self-administered questionnaire.

Of the 2,248 eligible cases, 320 (14%) died before we could interview them, 127 (6%) could not be found, 16 (1%) had moved out of the area, and 57 (3%) had physician refusals. We contacted the remaining 1,728, but 274 (16%) declined to be interviewed and 133 (8%) never answered or were not interviewed because of illness, impairment or other reasons. Thus, 1,321 eligible cases were interviewed for a participation rate of 76% and an overall response rate of 59% among the cases. The response rates within pathologic subgroups were 67% for follicular, 51% for diffuse, 47% for T cell, and 60% for other/unknown type of NHL cases.

Of the 2,409 eligible controls, 28 (1%) died before contact, 311 (13%) could not be located, and 24 (1%) had moved out of the area. We contacted the other 2,046, but 839 (41%) declined to be interviewed and 150 (6%) never answered or were not interviewed because of illness, language, or other reasons. Thus, 1,057 eligible controls were interviewed for a participation rate of 52% and an overall response rate of 44%. Case and control participation and response rates were highest in Iowa, higher in women than men, and higher in White subjects than others.

The present analysis of family history involved 689 cases and 535 controls who filled out the detailed self-administered family history questionnaire.

Statistical Methods. We used two methods to assess the association between risk of NHL and family history of the disease (20). In the first approach, we fitted logistic regression models with case-control status of the participating subjects as the outcome and family history of the subjects as the predictor. To examine the association between NHL and family history of a specific cancer, we defined family history as a binary variable indicating the presence or absence of any first-degree family member having the given cancer. The odds ratio [OR; approximately the same as relative risk (RR) for rare diseases] estimate, associated with family history of NHL (or any other cancer) in this analysis, gives a measure of familial aggregation of NHL (or any other cancer). Because of the detailed family history data available from this study, we could examine familial aggregation of NHL with not only hematolymphoproliferative cancers but also a variety of other cancers. The interpretation of the statistical significance of the aggregation between NHL and individual other cancers, however, requires caution because of the large number of comparisons we make. To address this multiple comparison problem, we also did a global analysis in which we examined the association between NHL and all other cancers together. In this analysis, for each NHL case and control, we counted

Table 1. Characteristics of cases and control*

	Control (%), n = 535	Case (%), n = 689
Gender		
Male	265 (49.5)	358 (52.0)
Female	270 (50.5)	331 (48.0)
Age (y)		
<35	32 (6.0)	36 (5.2)
35–44	56 (10.5)	75 (10.9)
45–54	110 (20.6)	149 (21.6)
55–64	126 (23.5)	185 (26.9)
65+	211 (39.4)	244 (35.4)
Study center		
Detroit	92 (17.2)	164 (23.8)
Iowa	122 (22.8)	171 (24.8)
Los Angeles	173 (32.3)	192 (27.9)
Seattle	148 (27.7)	162 (23.5)
Race		
African American	110 (20.6)	70 (10.2)
White	390 (72.9)	566 (82.1)
Other/unknown	35 (6.5)	53 (7.7)
Mean no. relatives		
Brothers	1.4	1.5
Sisters	1.5	1.5
Sons	1.2	1.2
Daughters	1.2	1.2
All relatives	7.3	7.4

*Restricted to subjects assigned to receive the detailed family history questionnaire.

the total number of other cancers the subject has in the family. If a relative had multiple other cancers, each of the cancers was counted separately. The association between NHL and total number of other cancers in family was examined using the logistic regression model.

This simple logistic regression model described above is the standard approach for analysis of family history data from case-control studies, but it fails to account for the family size and structure of each respondent and neglects the information inherent in the affected relative's age at onset. We therefore used a second approach that treats each relative of the study participants as a study unit and examines the difference between age-specific incidence of various cancers between relatives of the cases and relatives of controls. Cases and controls who filled out the detailed family history questionnaire provided detailed disease history information, including the age at onset and the current age for each of their first-degree relatives. We considered these relatives as a cohort of subjects who were followed from their birth until the incidence of the cancer of interest or the censoring age (i.e., the age of the relative at the time of the study or age at mortality if the relative died before the study took place). Standard methods for cohort data analysis, such as Kaplan-Meier plots and Cox proportional hazard regression models, were used to examine differences in the incidence of different cancers between the cohort of the relatives of cases and the cohort of the relatives of controls. Because each relative is considered as a study unit in this approach and the case-control status of the index study participant is treated as his/her family history, the family history variable in this approach always corresponds to one relative; thus, the problem of varying number of relatives does not arise. In this cohort analysis approach, we also examined whether early/late age at onset of NHL (defined as ≤50 or >50 years) could be a stronger predictor of risk of cancers in the relatives by considering three groups of relatives: relatives of controls, relatives of cases with age at onset of NHL ≤50 years, and relatives of cases with age at onset of NHL >50 years. SEs and 95% confidence intervals (95% CI) of variable estimates were obtained using robust methods (21) that can account for potential correlation between the relatives of the same subject. For tests of association, we reported the P for the robust score (RS) test, which is known to perform better than standard Wald test (equivalent to whether 95% CI includes the null value) for small sample sizes. All tests were two sided.

Results

Table 1 shows the demographic characteristics of the cases and controls who completed the detailed self-administered family history questionnaire. The proportion of African American subjects was lower in cases than in controls (10.2% versus 20.6%), whereas the distribution of the other characteristics was similar in cases and controls.

Table 2 shows the estimated OR of NHL associated with a family history of various hematolymphoproliferative cancers as estimated by logistic regression with adjustment for age, race, sex, center, and number of first-degree relatives (approach 1: case-control analysis). A positive family history of NHL was associated with a 2-fold increased risk of NHL. The estimate of familial aggregation from this approach, however, was not statistically significant. Based on the formula of population attributable fraction as $\Pr(\text{Exposure}|D = 1) \times (1 - 1 / \text{RR})$ (22), we estimated that approximately 1.4% of the cases in the population could be attributed to family history of NHL or lymphomas not otherwise specified.

Figure 1 shows the Kaplan-Meier incidence curves for four hematolymphoproliferative cancers among first-degree relatives of cases and controls and Table 3 shows the corresponding hazard ratio (HR) estimates from proportional hazard models (approach 2: cohort analysis). The estimated cumulative incidence of NHL at all ages

Table 2. NHL cases compared with NHL controls: OR for NHL according to family history of hematolymphoproliferative cancers

	Controls	Cases	OR*	95% CI
No multiple myeloma/ Hodgkin's lymphoma/ NHL/leukemia	372	490	1.00	Reference
NHL	5	16	2.06	0.73–5.76
Lymphoma not otherwise specified	6	11	1.17	0.42–3.23
NHL or lymphoma not otherwise specified	11	27	1.56	0.75–3.22
Hodgkin's lymphoma	5	11	1.67	0.55–5.05
Leukemia	18	25	1.12	0.59–2.13
Multiple myeloma	7	4	0.47	0.13–1.67
NHL/Hodgkin's lymphoma/multiple myeloma/leukemia	40	64	1.17	0.76–1.81

*Adjusted for age, sex, race, center, and number of relatives.

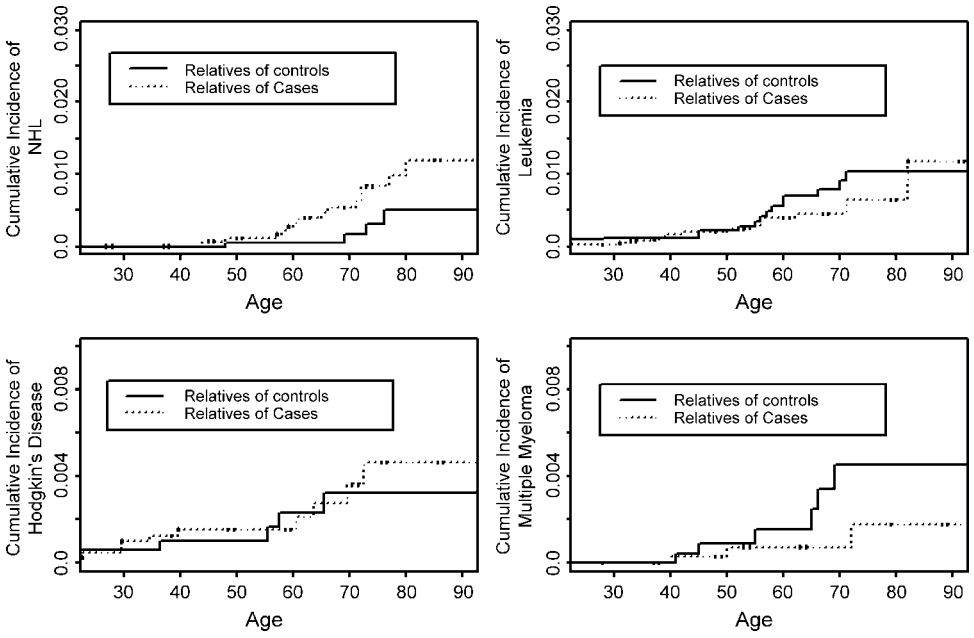

Figure 1. Cumulative incidence of hematolymphoproliferative cancers among first-degree relatives of NHL cases and NHL controls.

was higher in the relatives of cases compared with the relatives of controls (HR, 2.85; 95% CI, 0.95–8.53; *P* for RS test, 0.04). Cumulative incidence of Hodgkin's lymphoma was slightly and nonsignificantly elevated in relative of cases compared with relatives of controls (HR, 1.27; 95% CI, 0.42–3.86; *P* for RS test, 0.66). No such elevation in risk was observed for leukemia (HR, 0.77; 95% CI, 0.39–1.53; *P* for RS test, 0.46) or multiple myeloma (HR, 0.38; 95% CI, 0.10–1.52; *P* for RS test, 0.18). These HR estimates did not change when we adjusted for sex, race, and birth year.

NHL status of the study participants seemed to be a predictor for risk of NHL in siblings (HR, 7.59; 95% CI, 0.98–58.8; *P* for RS test, 0.012) but not for parents or offspring (HR, 1.26; 95% CI, 0.30–5.27; *P* for RS test, 0.75). When we grouped NHL and unspecified lymphomas together, a similar pattern of sibling-specific risk was observed (Table 3). NHL status of the study participants also seemed to be predictor for risk of NHL in men (HR, 6.19; 95% CI, 0.77–50.0; *P* for RS test, 0.03) but not in women (HR, 1.75; 95% CI, 0.46–6.74; *P* for RS test, 0.39). A similar pattern of male-specific risk was also observed for NHL and unspecified lymphomas combined (Table 3).

Table 4 shows estimated HRs associated with different hematolymphoproliferative cancers stratified by characteristics of cases. No appreciable difference in risk for NHL in relatives was observed by age at onset of the cases. The risk of Hodgkin's lymphoma seems to be elevated for the relatives of younger cases (HR, 3.19; 95% CI, 0.88–11.6; *P* for RS test, 0.15), although the result did not achieve statistical significance. Risk of NHL seems to be stronger for relatives of cases with follicular than with diffuse NHL, but this pattern of heterogeneity was much less prominent when NHL and unspecified lymphomas were combined in the relatives. It was difficult to estimate the risks of Hodgkin's lymphoma, leukemia, and multiple myeloma among relatives according to the pathologic subtypes of NHL in the cases because of small numbers.

Table 5 shows the estimated RR of NHL associated with a family history of 20 other cancers as estimated by logistic regression (approach 1). The risk of NHL was modestly elevated with a family history of a variety of different cancers; these individual associations, however, were not statistically significant, except marginally for

Table 3. Relative of NHL cases compared with relatives of NHL controls: HRs for hematolymphoproliferative cancers according to characteristics of the relatives

	NHL	NHL/lymphoma not otherwise specified	Hodgkin's lymphoma	Leukemia	Multiple myeloma
All first degree	2.85 (0.95–8.53)	1.71 (0.84–3.47)	1.27 (0.42–3.86)	0.77 (0.39–1.53)	0.38 (0.10–1.52)
Relative type					
Parents/children	1.26 (0.30–5.27)	1.00 (0.43–2.37)	1.73 (0.53–5.60)	0.71 (0.31–1.61)	0.46 (0.11–1.91)
Siblings	7.59 (0.98–58.8)	3.74 (0.81–17.4)	0.36 (0.03–4.03)	0.95 (0.26–3.54)	NA
Relative gender					
Female	1.75 (0.46–6.74)	1.17 (0.48–2.83)	0.58 (0.13–2.58)	0.77 (0.27–2.18)	0.13 (0.02–1.05)
Male	6.19 (0.77–50.0)	3.38 (0.97–11.8)	2.66 (0.56–12.7)	0.77 (0.31–1.93)	NA

NOTE: NA, estimates were not available or unstable due to small numbers.

Table 4. Relatives of NHL cases compared with relatives of NHL controls: HRs for hematolymphoproliferative cancers according to characteristics of the cases

Case characteristics	NHL	NHL/lymphoma not otherwise specified	Hodgkin's lymphoma	Leukemia	Multiple myeloma
Age at onset (y)					
≤50	2.37 (0.46–12.2)	1.64 (0.52–5.15)	3.19 (0.88–11.6)	0.49 (0.11–2.10)	NA
>50	2.94 (0.96–8.96)	1.72 (0.84–3.56)	0.80 (0.22–2.84)	0.83 (0.41–1.68)	0.47 (0.12–1.86)
Pathology group					
T cell	NA	NA	NA	0.68 (0.09–5.25)	1.76 (0.22–14.2)
Diffuse	1.34 (0.25–7.15)	1.56 (0.61–4.02)	1.32 (0.31–5.66)	0.66 (0.22–1.95)	NA
Follicular	4.45 (1.27–15.6)	2.00 (0.81–4.95)	2.00 (0.52–7.67)	1.12 (0.45–2.84)	NA
Other/unknown	3.37 (0.99–11.4)	1.93 (0.85–4.40)	0.99 (0.23–4.26)	0.62 (0.23–1.68)	0.66 (0.13–3.27)

NOTE: NA, estimates were not available or unstable due to small numbers.

prostate and stomach cancer. Using the cohort analysis approach (approach 2), we found stronger evidence for an increased risk of melanoma of the skin (HR, 2.89; 95% CI, 1.08–7.75; *P* for RS test, 0.02) and pancreas cancer (HR, 2.06; 95% CI, 0.96–4.43, *P* for likelihood ratio test, 0.05) among relatives of cases compared with relatives of controls. Some of these individual associations, however, may have occurred due to chance because of the large number of significance tests. Table 6 shows the RR of NHL (approach 1) associated with family history of all other cancers combined. We observed a 50% higher likelihood that cases would report three or more of the other cancers in their family (OR, 1.51; 95% CI, 0.87–2.62); the *P* for trend test was 0.09.

Discussion

In summary, our findings agree with other reports (8, 10-15) of NHL aggregating within families. Our data suggest that familial risk for NHL may be specific to siblings and to men. We find some evidence for increased risk of Hodgkin's lymphoma for relatives of early-onset NHL cases. We found no evidence of aggregation of NHL with leukemia or multiple myeloma in this study. Analysis of various other cancers provides modest evidence for familial aggregation of NHL with melanoma of the skin, stomach cancer, pancreatic cancer, and prostate cancer. Analysis of risk of NHL by family history of all other cancers together suggested a possible association between the risk of NHL and the total number of other cancers in family, but the possibility of differential recollection of reporting cannot easily be dismissed.

This study had several strengths. With its population-based design, the estimates of the RR associated with family history should represent the general population, allowing estimate of the population attributable fraction. Another strength was the availability of detailed data on dates of birth, death, and cancer occurrence in all family members. This detailed family history information enabled us to account for the number of relatives and to use the valuable information conveyed by the age at onset.

On the other hand, there are several limitations of the study. The small number of subjects with a family history of each specific type of cancer resulted in wide 95% CI for risk estimates. In addition, due to these small numbers, we could not study race-specific familial aggregation patterns. Family history of cancer relied on self-report, so differential recall of family history by cases and controls could have introduced bias into our estimation of RR. Other reports of recalling cancers in first-degree relatives suggest that reporting is fairly complete and accurate for cancers in general and for lymphoma in particular (23).

Table 5. NHL cases compared with NHL controls: other cancers reported on detailed family history (more than one could be mentioned per case-control subjects)

	Controls	Cases	OR*	95% CI	Pr > χ^2
Brain and other nervous system	14	17	0.80	0.38–1.68	0.56
Female-breast	54	76	1.04	0.70–1.53	0.85
Cervix uteri	13	8	0.43	0.17–1.08	0.07
Colon/rectum	46	53	0.80	0.52–1.24	0.31
Corpus uteri	11	16	1.02	0.46–2.26	0.96
Esophagus	2	6	2.28	0.45–11.5	0.32
Kidney/renal pelvis	8	15	1.19	0.49–2.89	0.70
Larynx	1	2	1.41	0.13–15.9	0.78
Liver and intrahepatic bile duct	11	19	1.27	0.59–2.77	0.54
Lung and bronchus	43	76	1.39	0.92–2.09	0.12
Melanoma of the skin	8	20	1.62	0.70–3.76	0.26
Oral cavity and pharynx	11	21	1.27	0.59–2.72	0.54
Ovary	10	15	0.99	0.43–2.28	0.98
Pancreas	11	26	1.67	0.80–3.49	0.18
Prostate	41	72	1.50	0.98–2.29	0.06
Stomach	12	29	1.94	0.96–3.93	0.07
Testis	5	3	0.46	0.11–1.97	0.29
Thyroid	2	5	2.59	0.49–13.8	0.27
Urinary bladder	6	12	1.39	0.51–3.78	0.53

*Adjusted for age, sex, race, center, and number of relatives.

Table 6. NHL cases compared with NHL controls: total number of other cancers reported on detailed family history

	Controls	Cases	OR*	95% CI
No. cancer in all relatives				
0	228	294	1.00	
1–2	203	278	1.05	0.81–1.37
3+	23	46	1.51	0.87–2.62
P for trend				0.09

*Adjusted for age, sex, race, center, and number of relatives.

Another limitation was that the high rate of nonresponse could have introduced bias if cases and controls differentially participated based on their family history. The estimate of risk from family history did not change appreciably when we adjusted for education level, a measure of social class likely to be related to response rate. Moreover, our findings remained similar when we restricted our analysis to only White subjects among whom the participation rate was higher for both cases (78%) and controls (55%). Consistency of our estimates with other studies also argues against a major response bias by family history.

Our overall finding of familial aggregation of NHL has been noted in other studies. A population-based case-control study in Iowa and Minnesota reported a significantly increased risk of NHL in individuals with a history of lymphoma in siblings (OR, 3.8; 95% CI, 1.3–11.5) but not with a history of lymphoma in parents (OR, 1.5; 95% CI, 0.5–4.2; ref. 11). A multicenter case-control study of men in the United States reported a significantly increased risk of NHL in individuals with a family history of lymphoma (OR, 3.0) as well as hematologic cancers (OR, 2.0; ref. 8). This study, however, found no significant difference in the effect of family history by type of relative. A case-control study in Yorkshire, United Kingdom reported a significantly increased risk of NHL in individuals with a family history of leukemia or lymphoma in first-degree relatives (OR, 4.0; ref. 10). None of the above case-control studies evaluated the separate effects of family history of NHL and Hodgkin's lymphoma on the risk of NHL and the sex-specific familial aggregation of these diseases. A hospital-based study in France reported increased incidence of Hodgkin's lymphoma in relatives of children with NHL compared with the general population, but the result did not achieve statistical significance (24).

Our results should also be compared with registry-based studies. Based on genealogy, cancer registry, and death certificates in the Utah Population Database, Cannon-Albright et al. (12) reported a familial aggregation of NHL, although their measure of familial aggregation is not directly comparable with either the OR or the HR estimate that we report in the current study. Using the same database, Goldgar et al. (13) compared observed numbers of cancer with expected numbers for the underlying Utah population. The resulting measure of standardized incidence ratio (SIR) is comparable with the HR we obtained in the cohort analysis approach for cancer incidence in the relatives (approach 2). This study reported an overall modest increase in risk of NHL among relatives of NHL cases (SIR, 1.68; 95% CI, 1.04–2.48) but noted that the aggregation to be present only for male (SIR, 3.18; 95% CI, 1.58–5.33) but not for female (SIR, 1.09; 95% CI, 0.20–2.66). Paltiel et al. (14) used cancer registry and family database in Israel to estimate the SIR for lymphoma among first-degree relatives of lymphoma cases to be 1.49 (95% CI, 0.91–2.31). These authors also reported a stronger elevation of risk for siblings (SIR, 2.68; 95% CI, 1.15–5.27). Dong and Hemminki (15) used a Swedish family cancer database to report the SIR for lymphoma in offspring and sibling of lymphoma patients to be 1.61 (95% CI, 1.16–2.26) and 2.26 (95% CI, 0.87–2.97), respectively. The latter two registry-based studies, however, did not investigate sex-specific familial aggregation. Goldin et al.[6] used familial data from a study based on linked cancer and population registries in Sweden and Denmark. The Swedish/Danish study includes ~70,000 first-degree relatives of >25,000 NHL cases. The authors computed HRs from survival analysis comparing the first-degree relatives of case probands with the first-degree relatives of matched control probands (same as approach 2 in our analysis). Pooled HRs for the two populations were obtained. Relatives of cases were at significantly increased risk for NHL (HR, 1.7; 95% CI, 1.39–2.16) and Hodgkin's lymphoma (HR, 1.4; 95% CI, 1.00–1.97).

In our study, we found no evidence of familial aggregation of NHL with leukemia and multiple myeloma. Only a few studies in the past have investigated these associations. A case-control study based in the United States (11) reported some evidence of increased risk of NHL with family history of leukemia (OR for parents, 1.9; 95% CI, 0.9–4.3; OR for sibling, 1.5; 95% CI, 0.6–3.1). A large registry-based study in Sweden (15), on the other hand, reported familial aggregation of lymphoma with myeloma (SIR for parents, 1.5; 95% CI, 1.05–2.11) but not with leukemia. The recent study of Goldin et al. quoted above found weak and nonsignificant increased risk of chronic lymphoid leukemia in relatives of NHL cases. Leukemia, like lymphoma, encompasses a wide variety of distinct malignancies; thus, the mixing of histologies of leukemia and lymphoma may well hide some strong associations between related histotypes. Exploration of those relationships requires a large number of cases and access to detailed medical records of relatives. Myeloma, another rare malignancy, also may have an association with NHL that was missed by current and other studies due to small numbers.

The pattern of male-specific and sibling-specific familial aggregation of NHL we observed in our study is intriguing. Several previous studies have also suggested such pattern familial aggregation for siblings (11, 15) and for males (13). These patterns, if confirmed in future studies, may provide important information on mechanisms of familial aggregation of NHL, including possible involvement of early environmental exposures and a role for X-linked or recessive genes (25). Previous study has reported familial aggregation of NHL to be similar for monozygotic and dizygotic twins (26), suggesting major role of environmental exposures that are shared between siblings.

We found a suggestion that NHL may aggregate with four specific other cancers: prostate, pancreas, stomach, and melanoma of the skin. Familial aggregation of NHL with prostate, pancreas, and stomach cancers has been reported in the past in other studies (11, 13). Moreover, several second cancer studies (27, 28) have reported the risk of melanoma to be higher among survivors of NHL cases than in the general population, suggesting a possible treatment effect and/or common etiologic factors. Two recent studies (15, 25) have reported familial aggregation (between same site) for prostate, stomach, and melanoma to be significantly higher for siblings than parent/offspring, a pattern similar to our findings

[6] Unpublished data.

for NHL. Two caveats apply. First, due to the large number of associations we tested, some of the site-specific positive findings arose by chance alone. Second, the nonspecificity of the association suggests that cases and controls may have differentially recalled and reported cancer. Risk of NHL may be associated with some nonhematologic cancers, but more research, especially from registries and cohort studies, is needed to confirm the association.

This report adds to the growing body of evidence on familial aggregation of NHL with hematolymphoproliferative and other cancers. Future research should consider the use of population-based and family-based studies to determine the inheritance pattern of NHL and to search for candidate genes. Population-based studies may be pooled to estimate familial risks more accurately and to determine which histologic types are likely to occur together. These and other studies suggest that only a small fraction of NHL is inherited. Further, familial aggregation may include some nongenetic contribution, but inherited susceptibility seems likely to account for some of the clustering within families. Finding the responsible genes may also shed light on the etiology of nonfamilial NHL.

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References

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1975-2000. Bethesda (MD): National Cancer Institute; 2003.
2. Hartge P, Devesa SS, Fraumeni JF Jr. Hodgkin's and non-Hodgkin's lymphomas. Cancer Surv 1994;19-20:423–53.
3. Manns A, Hisada M, La Grenade L. Human T-lymphotropic virus type I infection. Lancet 1999;353:1951–8.
4. Mueller NE, Mohar A, Evans A. Viruses other than HIV and non-Hodgkin's lymphoma. Cancer Res 1992;52 Suppl 19:5479S–81S.
5. Melbye M, Trichopoulos D. Non-Hodgkin's lymphoma. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of cancer epidemiology. New York: Oxford University Press; 2002.
6. Cerhan JR, Wallace RB, Folsom AR, Potter JD, Sellers TA, Zheng W, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst 1997;89:314–8.
7. Hirano K, Yamashita K, Yamashita N, Nakatsumi Y, Etsumi H, Kawashima A, et al. Non-Hodgkin's lymphoma in a patient with probable hereditary nonpolyposis colon cancer: report of a case and review of the literature. Dis Colon Rectum 2002;45:273–9.
8. Zhu K, Levine RS, Gu Y, Brann EA, Hall I, Caplan LS, et al. Non-Hodgkin's lymphoma and family history of malignant tumors in a case-control study (United States). Cancer Causes Control 1998;9: 77–82.
9. Chiu BC, Weisenburger DD, Cantor KP, Zahm SH, Holmes SH, Burmeister LF, et al. Alcohol consumption, family history of hematolymphoproliferative cancer, and the risk of non-Hodgkin's lymphoma in men. Ann Epidemiol 2002;12:309–15.
10. Cartwright RA, McKinney PA, O'Brien C, Richards ID, Roberts B, Lauder I, et al. Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. Leuk Res 1988;12:81–8.
11. Pottern LM, Linet M, Blair A, et al. Familial cancers associated with subtypes of leukemia and non-Hodgkin's lymphoma. Leuk Res 1991; 15:305–14.
12. Cannon-Albright LA, Thomas A, Goldgar DE, Gholami K, Rowe K, Jacobsen M, et al. Familiality of cancer in Utah. Cancer Res 1994;54:2378–85.
13. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994;86:1600–8.
14. Paltiel O, Schmit T, Adler B, Rachmilevitz EA, Polliack A, Cohen A, et al. The incidence of lymphoma in first-degree relatives of patients with Hodgkin disease and non-Hodgkin lymphoma: results and limitations of a registry-linked study. Cancer 2000;88:2357–66.
15. Dong C, Hemminki K. Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. Int J Cancer 2001;92:144–50.
16. Ward MH, Zahm SH, Weisenburger DD, Gridley G, Cantor KP, Saal RC, et al. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer Causes Control 1994;5:422–32.
17. Zahm SH, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A. The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. Arch Environ Health 1993; 48:353–8.
18. Zhu K, Levine RS, Brann EA, Gu Y, Caplan LS, Hall I, et al. Risk factors for non-Hodgkin's lymphoma according to family history of hematolymphoproliferative malignancies. Int J Epidemiol 2001;30: 818–24.
19. Casady RJ, Lepkowski JM. Stratified telephone survey designs. Surv Methodol 1993;19:103–13.
20. Liang KY, Pulver AE. Analysis of case-control/family sampling design. Genet Epidemiol 1996;13:253–70.
21. Lin DY, Wei LJ. The robust inference for the Cox proportional hazard model. J Am Stat Assoc 1989;84:1074–8.
22. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904–14.
23. Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. Am J Prev Med 2003;24:190–8.
24. Le Bihan C, Moutou C, Chompret A, Abel A, Poisson N, Brugiers L, et al. Cancers in relatives of children with non-Hodgkin's lymphoma. Leuk Res 1996;20:181–6.
25. Hemminki K, Vaittinen P, Dong C, Easton D. Sibling risks in cancer: clues to recessive or X-linked genes? Br J Cancer 2001;84:388–91.
26. Mack TM, Cozen W, Shibata DK, Weiss LM, Nathwani BN, Hernandez AM, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. N Engl J Med 1995;332:413–8.
27. Travis LB, Curtis RE, Boice JD Jr, Hankey BF, Fraumeni JF Jr. Second cancers following non-Hodgkin's lymphoma. Cancer 1991;67: 2002–9.
28. Brennan P, Coates M, Armstrong B, Colin D, Boffetta P. Second primary neoplasms following non-Hodgkin's lymphoma in New South Wales, Australia. Br J Cancer 2000;82:1344–7.